Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A method for producing at least one high temperature resistant yeast cell, the method comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell such that the at least one DNA polymerase provides mismatched bases at a frequency of 10^{-6} or greater;

wherein the at least one DNA polymerase is expressed in the at least one yeast cell with a plasmid expression vector; and

selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

2. (Canceled)

3. (Withdrawn) A method according to claim 2, wherein at least about 30% of the error-prone frequency agents have a lesser error-prone frequency.

4. (Canceled)

5. (Withdrawn) A method according to claim 1, wherein the agent having the lesser error-prone frequency is substantially error-free.

6.-8. (Canceled)

9. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site in at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of a DNA polymerase selected from the group consisting of a DNA polymerase that is innate to the at least one yeast cell and is capable of removing abnormal bases and a DNA polymerase that is innate to the at least one yeast cell and is capable of repairing mismatched base pairs.

10.-11. (Canceled)

12. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site in a DNA polymerase that has a proofreading function.

13. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of a DNA polymerase selected from the group consisting of DNA polymerase α, DNA polymerase β, DNA polymerase γ, DNA polymerase δ, and DNA polymerase ε of eukaryotic cells.

14. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase selected from the group consisting of DNA polymerase δ and DNA polymerase ε of eukaryotic cells, wherein modifying at least one

amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase alters proofreading activity of the at least one DNA polymerase.

15. (Canceled)

16. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises introducing an exogenous DNA polymerase into the at least one yeast cell, wherein the exogenous DNA polymerase is a DNA polymerase variant having at least one modified amino acid position in a 3' to 5' exonuclease active site.

17. (Previously presented) A method according to claim 16, wherein the step of introducing the exogenous DNA polymerase into the at least one yeast cell comprises introducing the exogenous DNA polymerase using a method selected from homologous recombination and transformation using gene introduction or a plasmid.

18.-31. (Canceled)

32. (Withdrawn) A method according to claim 1, wherein the cell is a mammalian cell.

33. (Previously presented) A method according to claim 1, wherein after the step of selecting and isolating the at least one high temperature resistant yeast cell, the at least one yeast cell has substantially the same growth as that of a wild type of the at least one yeast cell.

34.-35. (Canceled)

36. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand.

37.-38. (Canceled)

39. (Withdrawn) A method according to claim 1, wherein the cell includes a cancer cell.

40. (Withdrawn) A method according to claim 1, wherein the cell constitutes a tissue.

41.-44. (Canceled)

45. (Currently amended) A method for producing at least one high temperature resistant yeast cell, comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell such that the at least one DNA polymerase provides mismatched bases at a frequency of 10^{-6} or greater, wherein the at least one DNA polymerase is expressed in a plasmid expression vector and is selected from DNA polymerase δ and DNA polymerase ε; and

selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

46.-47. (Canceled)

48. (Withdrawn) A method according to claim 45, wherein at least about 30% of the error-prone frequency agents have a lesser error-prone frequency.

49. (Canceled)

50. (Withdrawn) A method according to claim 45, wherein the agent having the lesser error-prone frequency is substantially error-free.

51. (Canceled)

52.-53. (Canceled)

54. (Previously presented) A method according to claim 45, wherein the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of a DNA polymerase is selected from the group consisting of a DNA polymerase that is innate to the at least one yeast cell and is capable of removing abnormal bases and a DNA polymerase that is innate to the at least one yeast cell and is capable of repairing mismatched base pairs.

55. (Previously presented) A method according to claim 45, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site in a manner that provides a difference in the number of replication errors between one strand and the other strand of double-stranded genomic DNA in the at least one yeast cell.

56.-60. (Canceled)

61. (Previously presented) A method according to claim 45, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises introducing an exogenous DNA polymerase into the at least one yeast cell, wherein the exogenous DNA polymerase is a DNA polymerase variant having at least one modified amino acid position in a 3' to 5' exonuclease active site.

62. (Previously presented) A method according to claim 61, wherein the step of introducing the exogenous DNA polymerase into the at least one yeast cell comprises introducing the exogenous DNA polymerase using a method selected from homologous recombination and transformation using gene introduction or a plasmid.

63.-76. (Canceled)

77. (Withdrawn) A method according to claim 45, wherein the cell is a mammalian cell.

78. (Previously presented) A method according to claim 45, wherein after the step of selecting and isolating the at least one high temperature resistant yeast cell, the at least one yeast cell has substantially the same growth as that of a wild type of the at least one yeast cell.

79.-80. (Canceled)

81. (Previously presented) A method according to claim 45, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at

least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand.

82.-83. (Canceled)

84. (Withdrawn) A method according to claim 45, wherein the cell includes a cancer cell.

85. (Withdrawn) A method according to claim 45, wherein the cell constitutes a tissue.

86.-94. (Canceled)

95. (Withdrawn) A method for producing a nucleic acid molecule encoding a gene having a regulated hereditary trait, comprising the steps of:

changing an error-prone frequency of gene replication of an organism;

reproducing the resultant organism;

identifying a mutation in the organism; and producing a nucleic acid molecule encoding a gene having the identified mutation.

96. (Withdrawn) A nucleic acid molecule, produced by a method according to claim 95.

97. (Withdrawn) A method for producing a polypeptide encoded by a gene having a regulated hereditary trait, comprising the steps of: changing an error-prone frequency of gene replication of an organism; reproducing the resultant organism; identifying a mutation in the organism; and producing a polypeptide encoded by a gene having the identified mutation.

98. (Withdrawn) A polypeptide, produced by a method according to claim 97.

99. (Withdrawn) A method for producing a metabolite of an organism having a regulated hereditary trait, comprising the steps of: changing an error-prone frequency of gene replication of an organism; reproducing the resultant organism; identifying a mutation in the organism; and producing a metabolite having the identified mutation.

100. (Withdrawn) A metabolite, produced by a method according to claim 99.

101. (Withdrawn) A nucleic acid molecule for regulating a hereditary trait of an organism, comprising: a nucleic acid sequence encoding a DNA polymerase having a regulated error-prone frequency.

102. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is DNA polymerase δ or ε of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria.

103. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is a variant of DNA polymerase δ or ε of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria, the variant comprising a mutation which deletes only a proofreading activity thereof.

104. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is a variant of DNA polymerase δ of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria, the variant comprising a mutation which deletes only a proofreading activity thereof.

105. (Withdrawn) A vector, comprising a nucleic acid molecule according to claim 101.

106. (Withdrawn) A cell, comprising a nucleic acid molecule according to claim 101.

107. (Withdrawn) A cell according to claim 106, wherein the cell is a eukaryotic cell.

108. (Withdrawn) A cell according to claim 107, wherein the eukaryotic cell is selected from the group consisting of plants, animals, and yeasts.

109. (Withdrawn) A cell according to claim 106, wherein the cell is a gram-positive bacterial cell.

110. (Withdrawn) A cell according to claim 106, wherein the cell is used for regulating a conversion rate of a hereditary trait.

111. (Withdrawn) An organism, comprising a nucleic acid molecule according to claim 101.

112. (Withdrawn) A product substance, produced by a cell according to claim 106 or a part thereof.

113. (Withdrawn) A nucleic acid molecule, contained in a cell according to claim 106 or a part thereof.

114. (Withdrawn) A nucleic acid molecule according to claim 113, encoding a gene involved in the regulated hereditary trait.

115. (Withdrawn) A method for testing a drug, comprising the steps of: testing an effect of the drug using a cell according to claim 106 as a model of disease; testing an effect to the drug using a wild type of the cell as a control; and comparing the model of disease and the control.

116. (Withdrawn) A method for testing a drug, comprising the steps of: testing an effect of the drug using an organism according to claim 111 as a model of disease; testing an effect to the drug using a wild type of the organism as a control; and comparing the model of disease and the control.

117. (Withdrawn) A set of at least two kinds of polymerases for use in regulating a conversion rate of a hereditary trait of an organism, wherein the polymerases have a different error-prone frequency.

118. (Withdrawn) A set according to claim 117, wherein one of the at least two kinds of polymerases is involved in an error-prone frequency of a lagging strand, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand.

119. (Withdrawn) A set according to claim 117, wherein the set of polymerases are derived from the same species.

120. (Withdrawn) A set of at /east two kinds of polymerases for use in producing an organism having a regulated hereditary trait, wherein the polymerases have a different error-prone frequency.

121. (Withdrawn) A set according to claim 120, wherein one of the at least two kinds of polymerases is involved in an error-prone frequency of a lagging strand, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand.

122. (Withdrawn) A set according to claim 121, wherein the set of polymerases are derived from the same organism species.

123. (Withdrawn) Use of at least two kinds of polymerases for regulating a conversion rate of a hereditary trait of an organism, wherein the polymerases have a different error-prone frequency.

124. (Withdrawn) Use of at least two kinds of polymerases for producing an organism having a regulated hereditary trait, wherein the polymerases have a different error-prone frequency.

125. (Withdrawn) A method for regulating a conversion rate of a hereditary trait of a yeast cell, wherein the cell has resistance to temperature, the resistance not being possessed by the cell before the conversion, the method comprising the steps of:

regulating the proofreading function of at least one DNA polymerase of the yeast by site-directed mutagenesis; and

subjecting the yeast to acclimation culture by gradually increasing culture temperature.

126. (Currently amended) A method for producing at least one high temperature resistant yeast cell, comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell such that the at least one DNA polymerase provides ~~at least one mismatched base pair in a base sequence~~ mismatched bases at a rate of 10^{-6} or greater, wherein the at least one DNA polymerase is selected from DNA polymerase δ and DNA polymerase ε and, wherein the at least one DNA polymerase is expressed in the at least one yeast cell

with a plasmid expression vector; and

selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

127. (Withdrawn) A method according to claim 126, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

128. (Withdrawn) A method according to claim 1, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

129. (Withdrawn) A method according to claim 45, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to

the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

130. (Currently amended) A method for producing a desired hereditary trait in at least one eukaryotic cell, the method comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell such that the at least one DNA polymerase provides mismatched bases at a frequency of 10^{-6} or greater;

wherein the at least one DNA polymerase is a DNA polymerase expressed in the at least one eukaryotic cell with a plasmid expression vector; and

selecting and isolating the at least one eukaryotic cell exhibiting the desired hereditary trait.

131. (Previously presented) The method of claim 130, wherein the at least one eukaryotic cell is selected from a yeast cell, a mammalian cell, an embryonic stem cell, a tissue, an organism, and a mouse.

132. (Canceled)

133. (Previously presented) A method according to claim 131, wherein the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of a DNA polymerase selected from the group consisting of a DNA polymerase that is innate to the at least one eukaryotic cell and is capable of removing abnormal bases and a DNA polymerase that is innate to the at least one eukaryotic cell and is capable of repairing mismatched base pairs.

134. (Previously presented) A method according to claim 132, A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand.

135. (Previously presented) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site in at least one DNA polymerase operable in at least one eukaryotic cell comprises

modifying at least one amino acid position in a 3' to 5' exonuclease active site in a DNA polymerase that has a proofreading function.

136. (Previously presented) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of a DNA polymerase selected from the group consisting of DNA polymerase α, DNA polymerase β, DNA polymerase γ, DNA polymerase δ, and DNA polymerase ε of eukaryotic cells.

137. (Previously presented) A method according to claim 132, wherein the step modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of the at least one DNA polymerase comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase selected from the group consisting of DNA polymerase δ and DNA polymerase ε of eukaryotic cells, wherein modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase alters proofreading activity of the at least one DNA polymerase.

138. (Canceled)

139. (Canceled)

140. (Currently amended) A method according to ~~claim 138~~ claim 130, wherein the ~~step of introducing an exogenous DNA polymerase variant comprises introducing a~~ at least one DNA polymerase is a DNA polymerase variant selected from a DNA polymerase variant derived from a species of eukaryotic organism that is the same as the at least one eukaryotic cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one eukaryotic cell.

141. (Previously presented) A method according to claim 16, wherein the step of introducing an exogenous DNA polymerase variant comprises introducing a DNA polymerase variant selected from a DNA polymerase variant derived from a species of yeast that is the same as the at least one yeast cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one yeast cell.

142. (Previously presented) A method according to claim 61, wherein the step of introducing an exogenous DNA polymerase variant comprises introducing a DNA polymerase variant selected from a DNA polymerase variant derived from a species of

yeast that is the same as the at least one yeast cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one yeast cell.

143. (Previously presented) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

144. (Previously presented) A method according to claim 45, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

145. (Previously presented) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

146. (Withdrawn) A method according to claim 130, further comprising, restoring the error prone frequency of DNA replication in the at least one eukaryotic cell to an error prone frequency exhibited during DNA replication in the at least one eukaryotic cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.